Functional Atlas of Orphan Nuclear Receptors

Purpose: Orphan Nuclear Receptors (ONRs) represent a branch of the Nuclear Receptor superfamily with several shared characteristics but distinct structures and emerging functional significance. They function as morphogens, and as intracellular regulators of metabolism, and key intermediates in biochemical pathways. The overall focus of the Functional Atlas of Orphan Nuclear Receptors will be to elucidate the role(s) played by ONRs in the development of a number of metabolic disorders, including Type 2 diabetes, obesity, hypertension, atherosclerosis, lipid dysregulation, and others, as well as in processes of aging and hormone-dependent cancers.

Goals: 1) Execute research strategies designed to rapidly and efficiently elucidate those facets of ONR biology most critical to its understanding; 2) To facilitate the generation of hypotheses, design of experiments and communication of results by scientists active in this field.

Strategy: Use emerging and novel methods to elucidate ONR function. Develop a web-accessible bioinformatics resource in which current and emerging information on ONRs will be organized into more accessible and "user-mineable" forms.

The Functional Atlas of Orphan Nuclear Receptors is a consortium agreement between the NIH (NIDDK, NIA, NCI) and 5 institutions (Baylor College of Medicine, Salk Institute, Duke University, University of Pennsylvania, UT Southwestern). The mechanism of support is a cooperative agreement comprising research projects and core resources.

Research Projects: Bridging Strands

1) Genomic and Metabolic Profiling of ONRs

This strand will integrate spatiotemporal distribution patterns of ONRs with target gene expression profiles to construct transcriptional and metabolic rationales for ONR function.

- a- Characterization of expression patterns of PPARs, PXR/SXR, LXR in adult mice
- b- Expression profiling of PPAR, PXR, LXR target genes in wild type and null mice and cultured cell lines
- c- Extend these analyses to other ONRs to establish a complete, integrated and freely accessible ONR and target gene database
- d- Determine the level of expression of CAR in mouse tissues
- e- Define the responses of known and newly identified CAR target genes to CAR activation and inactivation and to loss of CAR expression in CAR-/- mice
- f- Profile expression of SHP and characterize regulation of SHP target genes
- g- Extend these profiles to other metabolically important ONRs

2) Proteomic Profiling of ONR Coregulators

This strand will establish mechanistic principles for ONR function. Specifically, characterization of ONR-associated coregulator complexes and their regulation, mapping of protein-protein interaction domains and identification of specific target gene networks.

a- Proteomics of coactivators
b- Proteomics of corepressors
c- Generation of peptide antagonists for functional mapping of ONRs and nuclear coregulators

Resources: Cores

A) Bioinformatics resource
NURSA: Nuclear Receptor Signaling Atlas (www.Nursa.org under construction)

B) Administrative resource
Steering committee and external advisory committee

C) Microarray resource
Provide a common infrastructure to facilitate a standardized approach towards the collection of nuclear receptor target gene information.

D) Expression profiling resource
Construct high-resolution expression and functional profiles for ONRs in order to elucidate the basis of their tissue and cell-specific functions (expression patterns at a cellular level).

Pilot and Feasibility studies (P&Fs):

1) Functional determinants in ONRs:
Identify the general and specific determinants of protein and ligand recognition in the ligand-binding domain of ONRs.

2) Chemical profiling of ONRs:
Develop small-scale cell-based assays to facilitate the rapid screening of large numbers of compounds against individual ONRs.